· Clinical Research ·

Receded near point of convergence as a predictor of mild cognitive impairment in the general geriatric population: results from a population-based study

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Abstract
● **AIM:** To investigate the relationship between near point of convergence (NPC) and mild cognitive impairment (MCI) in the general elderly population.

● **METHODS:** The present report is a part of the Tehran Geriatric Eye Study (TGES): a population-based cross-sectional study conducted on individuals 60 years of age and above living in Tehran, Iran using the multi-stage stratified random cluster sampling method. Cognitive status was assessed using the Persian version of the Mini-Mental State Examination (MMSE). All study participants underwent complete ocular examination including measurement of uncorrected and best-corrected visual acuity, objective and subjective refraction, cover testing, NPC measurement, and slit-lamp biomicroscopy.

● **RESULTS:** The data of 1190 individuals were analyzed for this report. The mean age of the participants analyzed was 66.82±5.42 (60-92y) and 728 (61.2%) of them were female. Patients with MCI had a significantly more receded NPC compared to subjects with normal cognitive status (10.89±3.58 *vs* 7.76±2.71 cm, $P<0.001$). In the multivariable logistic regression model and in the presence of confounding variables, a receded NPC was statistically significantly associated with an increased risk of MCI (odds ratio: 1.334, 95% confidence interval: 1.263 to 1.410, $P<0.001$). According to receiver operating characteristic (ROC) analysis, a cut point NPC> 8.5 cm (area under the curve: 0.764, $P<0.001$) could predict the presence of MCI with a sensitivity and specificity of 70.9% and 69.5%, respectively.

● **CONCLUSION:** A receded NPC can be clinically proposed as a predictor of MCI in older adults. It is recommended that elderly with a receded NPC>8.50 cm undergo detailed cognitive screening for a definite diagnosis of MCI. In this case, the necessary interventions can be carried out to slow down MCI progression to dementia.

● **KEYWORDS:** near point of convergence; mild cognitive impairment; geriatrics; population-based study
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INTRODUCTION

Cognitive impairment is described as the decline of one or more cognitive domains and is classified into mild cognitive impairment (MCI) and dementia depending on the severity[1]. The MCI is characterized as a transition stage between cognitive changes of normal aging process and early dementia without significant impacts on activities of daily living[2]. The MCI prevalence in older adults aged above 60y has been reported between 5.13% and 29.9% depending on the diagnostic criteria and the studied population demographics, with an annual incidence of 3.2–104.6 per 1000 individuals[3]. According to previous studies, MCI patients deteriorate to dementia usually Alzheimer's disease (AD) at an annual rate of 10%-15%, and about 80% develop AD after 6y[4-5]. Cognitive impairment leads to serious consequences such as social isolation, increased risk of mortality, and reduced quality of life[6-7]. Moreover, cognitive impairment imposes a significant economic burden on societies and patients' families[8]. Timely diagnosis of cognitive impairment is crucial for interventions to prevent or slow its progression[9]. Although there is currently no approved pharmaceutical treatment for cognitive impairment, some measures such as the use of cholinesterase inhibitors[10], physical exercise[11], cognitive rehabilitation[12], social engagement[13], nutritional and antioxidant supplements[14], and managing modifiable risk factors (*e.g.*, diabetes, hypertension, overweight, smoking)[15] have shown promising results in controlling the progression of MCI to dementia. The MCI diagnosis is mainly based on the patient's history and cognitive examination *via* some questionnaires particularly Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE)[16]. Although these questionnaires are well-known tools for cognitive assessment, they have limitations. These are subjective instruments highly dependent on the quality of patient's responses and their application in geriatrics may be difficult due to poor motivation, lack of cooperation, and poor literacy[16]. In addition, these tools are primarily used in research studies and have limited use in routine health-related examinations for the elderly. Therefore, it would be helpful to find simple and preferably objective routine clinical methods to help identify MCI.

Near point of convergence (NPC) refers to the maximum convergence capability of the eyes and consists of four distinct elements including tonic convergence, proximal convergence, accommodative convergence, and fusional convergence[17]. A receded NPC is the most important clinical sign used by optometrists to diagnose convergence insufficiency; the most prevalent binocular vision anomaly, especially in the elderly population[17]. There is some evidence in the literature indicating a receded NPC could be related to an increased risk of cognitive impairment in especial groups such as patients with Parkinson's disease (PD) and those with sport-related concussion[18-20]. To the best of our knowledge, there is no population-based study on the relationship between NPC and cognitive impairment in the elderly population. Some theories can be proposed for this relationship, including common pathogenesis, sensory deprivation caused by diplopia, and avoiding visual activities that stimulate cognitive performance. So, the present report aimed to evaluate this relationship in a large population-based sample of the Iranian elderly population.

SUBJECTS AND METHODS

Ethical Approval This study followed the tenets of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Iran University of Medical Sciences (ethics code: IR.IUMS.REC.1400.858). Written informed consent was obtained from all participants.

Study Design, Sampling, and Preliminary Evaluation This report relates to a large cross-sectional population-based study (Tehran Geriatric Eye Study) conducted using a stratified random cluster sampling on elderly residents of Tehran (the capital of Iran) aged 60y and above in 2019. Tehran's twenty-two municipal districts were defined as strata, and the census population ≥60y in different districts was inquired from the Iranian Statistics Center. Next, we prepared the block maps of districts and each block was defined a cluster. A total of 160 clusters (each cluster contained 20 people) were randomly selected from 22 districts in a proportional to size manner. After the desired clusters were identified, a sampling team visited their addresses and the first house on southwest sector of each cluster (block) was selected as the cluster head; the next households were selected through a counterclockwise movement. During sampling process, all individuals ≥60y were invited to the study. The study goals were fully elaborated to all invitees and they were assured of the data confidentiality. If a person desired to participate, we obtained informed consent, and an ID card was issued. This process continued until the required sample size was completed in each cluster. The participants were transported to the examination site free of charge within a pre-determined day.

Once the study participants presented to the examination site, information on education level, living status, history of systemic and ocular diseases, history of stroke, previous ocular surgery, use of systemic and ocular medications, and health-related behaviors including smoking were collected through a preliminary interview. In the next step, the body mass index (BMI) was calculated following measurements of weight and height using the formula: weight (kg)/height (m)^2. The blood pressure was measured using sphygmomanometry (OMRON, HEM-2228-E, Kyoto, Japan) and blood samples were taken for laboratory tests to measure glycosylated hemoglobin (HbA1c) and cholesterol levels.

Cognitive Evaluation Cognitive performance was evaluated using the Persian version of the MMSE questionnaire. The MMSE is a well-known and common screening test for general cognitive evaluation whose validity and reliability have been confirmed by various studies[21]. This questionnaire consists of 11 items evaluating major cognitive domains, including: orientation to time (question 1; 5 points), orientation to place (question 2; 5 points), registration (question 3; 3 points), attention and calculation (question 4; 5 points), recall (question 5; 3 points), language (question 6; 2 points, question 7; 1 point, question 8; 3 points, question 9; 1 point, question 10; 1 point), and copying (question 11; 1 point). The questionnaire's total score would range from 0 to 30, with a lower score representing more severe impairment. The scores ≥24 points are considered "normal" cognitive performance, whereas scores below this indicate MCI (18 to 23 points), or severe cognitive impairment (0 to17 points)[22-23].

Ocular Examination Uncorrected and presenting distance visual acuities (UCVA and PVA) were measured using an electronic chart (Smart LC 13, Medizs Inc., Korea) at 6 m, followed by objective refraction using an auto-refractometer/keratometer (ARK-510A, Nidek Co. 42 LTD, Aichi, Japan), and subjective refraction to obtain optimal distance refractive correction and the best-corrected distance visual acuity (BCVA). Near subjective refraction was also performed to determine the power of near addition lenses. The binocularity was checked using cover/uncover and alternating cover tests at far (6 m) and near (40 cm), respectively and any motor deviation (heterotropia or heterophoria) was detected and measured using an alternating prism cover test. The cover test at near was performed with the near addition lenses in place.

In the next step, the NPC was tested through near refractive correction (distance correction+addition lenses). The target used was a single character on the near acuity chart one line above the BCVA in the worse eye. The target slowly approached the participant along the midline from a 50 cm distance at a rate of 1-2 cm/s. The subject was asked to try to keep the target single as much as possible and to report whenever the target became sustainably double (could not recovered to single with further effort). At the point where the examinee reported sustained diplopia or the examiner noticed binocular fusion loss, the target's distance was accurately measured from the spectacle plane using a 50 cm ruler and recorded as NPC. To improve the test reliability, the measurement was performed five times and the mean of five measurements was recorded as the final result. Finally, all study subjects underwent slit-lamp examination (B900, Haag-Streit AG, Bern, Switzerland) by an ophthalmologist. Examination of the posterior segment was performed using a +90 diopter lens.

Exclusion Criteria Exclusion criteria were BCVA worse than 20/30 in either eye, heterotropia, amblyopia, history of intraocular surgery such as cataract or retinal surgery, any ocular disease affecting binocularity, a history of ocular trauma, use of ocular or systemic drugs affecting binocularity, previous diagnosis of dementia and its causes (*e.g.*, PD, AD), severe cognitive impairment (MMSE score <18), and missing data.

Definitions The MCI was defined as an MMSE score between 18 and 23[22-23]. Diabetes mellitus (DM) diagnostic criteria were the participant's self-report, use of hypoglycemic medication, or HbA1c≥6.5%[24]. The diagnostic criteria of systemic hypertension (HTN) were the participant's self-report, use of HTN medication, or systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg[25]. Hypercholesterolemia (HC) was defined based on the self-report, use of cholesterol-lowering medication, or a blood total cholesterol level >200 mg/dL[26]. Smoking at least one cigarette per day for at least the last 6mo was defined as current smoking.

Statistical Analysis Statistical Package for the Social Sciences (SPSS) version 26 was used for statistical analysis. The cluster sampling effect was considered for confidence interval calculation. We applied simple, age and sex-adjusted, and multivariable-adjusted logistic regression models to investigate the relationship between NPC (exposure) and MCI (outcome), and reported the odds ratios (ORs) with 95% confidence interval (CI) values. The potential confounders considered based on the literature were age, sex, BMI, DM, HTN, history of stroke, current smoking, HC, education level (years of education), living status (living alone and not living alone), refractive error, and PVA in the better eye. The real confounding variables in the dataset were identified using manual backward multiple logistic regression analysis with $P>0.20$ as a criterion for elimination from the model. The discriminate ability of the NPC between MCI and normal cognitive performance was assessed using the receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC). Moreover, the sensitivity and specificity were calculated by setting an optimal threshold using the ROC analysis. P values less than 0.05 were considered statistically significant.

RESULTS

Of the 3791 people invited, 3310 participated in the Tehran Geriatric Eye Study (response rate: 87.3 percent). The data of 1190 individuals were analyzed in this report after applying the exclusion criteria. The reasons for exclusion were BCVA worse than 20/30, amblyopia or ocular disease: 585, history of ocular trauma: 22, strabismus: 115, history of intraocular surgery: 751, use of drugs affecting binocularity: 44, physical inability to comply with testing: 9, previous diagnosis of dementia or severe cognitive impairment (MMSE score<18): 294, and missing data: 300. The mean age of the participants analyzed was 66.82±5.42 (60-92y) and 728 (61.2%) of them were female.

Table 1 presents the sample characteristics based on cognitive status. According to Table 1, patients with MCI were significantly older and had a higher BMI, a higher prevalence of DM, a lower education level, worse PVA in the better eye, and less hyperopic spherical equivalent refraction compared to those with normal cognitive performance (all $P<0.05$). History of stroke was significantly more prevalent in people without MCI compared to those with MCI ($P=0.006$). Moreover, patients with MCI had a significantly more receded NPC compared to subjects with normal cognitive status (10.89±3.58 *vs* 7.76±2.71 cm, $P<0.001$).

Table 2 presents the results of the final adjusted backward-stepwise multiple logistic regression model for the associations of potential confounders with MCI. As seen in Table 2, all variables maintained in the final model had a P value <0.2 and could be considered a real confounder in the dataset.

Table 1 Characteristics of the study sample based on cognitive status

Characteristic	No cognitive impairment (*n*=891)		Mild cognitive impairment (*n*=299)		*P*
	n (%)	Mean±SD[a]	*n* (%)	Mean±SD	
Age (y)	-	66.11± 5.18	-	68.95±5.57	<0.001[b]
Sex (female)	534 (59.93)	-	194 (64.88)	-	0.073
Body mass index (kg/m^2)	-	28.76± 4.91	-	29.80± 4.44	0.001[b]
Diabetes mellitus	213 (23.90)	-	97 (32.44)	-	0.002[b]
Systemic hypertension	226 (25.36)	-	65 (21.74)	-	0.243
Hypercholesterolemia	238 (26.71)	-	84 (28.09)	-	0.260
History of stroke	168 (18.85)	-	37 (12.37)	-	0.006[b]
Current smoking	134 (15.04)	-	34 (11.37)	-	0.068
Education level (years of education)	-	10.26± 4.60	-	5.15± 3.49	<0.001[b]
Living status (alone)	82 (9.20)	-	30 (10.03)	-	0.311
BCVA in the better eye (logMAR)	-	0.08± 0.008	-	0.09± 0.009	0.091
PVA in the better eye (logMAR)	-	0.19±0.002	-	0.21±0.002	<0.001[b]
SE of objective refraction in the right eye (D)	-	0.71±1.17	-	0.56±1.01	0.045[b]
Near point of convergence (cm)	-	7.76± 2.71	-	10.89±3.58	<0.001[b]

BCVA: Best-corrected distance visual acuity; PVA: Presenting distance visual acuity; SE: Spherical equivalent; MAR: Minimum angle of resolution. [a]Number (%) was reported for categorical variables and mean±SD was reported for continuous variables; [b]Statistically significant (*P*<0.05).

Table 2 The final adjusted backward-stepwise multiple logistic regression model for the associations of potential confounders with mild cognitive impairment

Variable	Odds ratio	95% confidence interval	*P*
Age (y)	1.073	1.043 to 1.103	<0.001
Body mass index (kg/m^2)	1.031	0.998 to 1.064	0.065
Diabetes mellitus	1.401	1.004 to 1.954	0.047
History of stroke	0.681	0.437 to 1.059	0.088
Education level (y)	0.765	0.735 to 0.796	<0.001
Spherical equivalent refraction (D)	0.878	0.760 to 1.015	0.078

Cox & Snell R square of the model: 0.241.

Table 3 Simple, age and sex-adjusted, and multivariable-adjusted associations of near point of convergence with mild cognitive impairment

Items	Mild cognitive impairment, OR (95%CI); *P*		
	Simple model	Age-sex adjusted model	Multivariable model[c]
Near point of convergence	1.352 (1.290 to 1.416); <0.001	1.354 (1.291 to 1.421); <0.001	1.334 (1.263 to 1.410); <0.001

[c]Adjusting for age, body mass index, diabetes mellitus, history of stroke, education level, and spherical equivalent refraction Cox & Snell *R* square of the multivariable model: 0.318.

Table 3 shows the simple, age and sex-adjusted, and multivariable-adjusted associations of NPC with MCI. In the simple and age-sex adjusted models, a receded NPC was statistically significantly related to an increased risk of MCI (ORs 1.352 and 1.354, 95%CIs: 1.290 to 1.416 and 1.291 to 1.421, respectively, both *P*<0.001). In the multivariable-adjusted model and in the presence of confounding variables, the association between NPC and MCI attenuated slightly but remained statistically significant (OR: 1.334, 95%CI: 1.263 to 1.410, *P*<0.001).

The results of ROC analysis showed that a cut point NPC> 8.5 cm (AUC: 0.764, P<0.001) can predict the presence of MCI with sensitivity and specificity of 70.9% and 69.5%, respectively. Figure 1 illustrates the ROC curve for the discriminant ability of NPC between MCI and normal cognitive status.

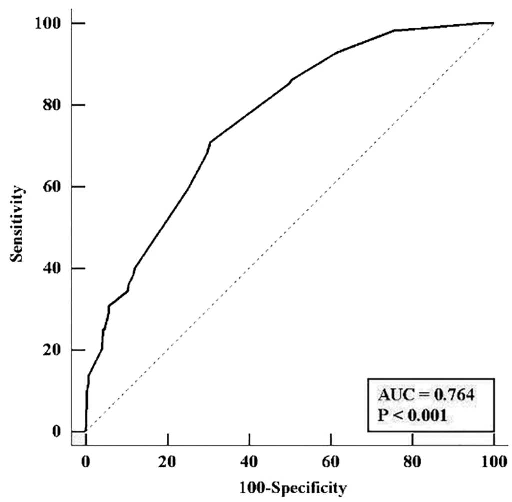

Figure 1 Receiver operating characteristic (ROC) curve for the discriminant ability of the near point of convergence between mild cognitive impairment and normal cognitive performance.

DISCUSSION

As mentioned earlier, there is some evidence in the literature about the relationship between a receded NPC and increased risk of cognitive impairment in especial groups. A recent study by Holden *et al*[18], investigated the relationship between NPC and cognitive status in patients with PD. The results showed that the mean NPC was significantly more receded in patients with cognitive impairment (18.4 cm), compared to those without cognitive impairment (12.5 cm). Pearce *et al*[19] evaluated the NPC in a sample of athletes after sport-related concussion. According to the results, athletes with a receded NPC had worse neurocognitive impairment than those with normal NPC. In another study performed by Naumann *et al*[20], the presence of diplopia in patients with PD was associated with cognitive impairment in visuospatial and visuoperceptive function. Since convergence insufficiency with intermittent diplopia is a common finding in PD[27], the results of Naumann *et al*'s study[20] can also draw attention to the relationship between a receded NPC and cognitive impairment.

To our best knowledge, the present report is the first one to investigate the association between NPC and MCI in a large sample of the general elderly population. The results showed a significant difference in the mean NPC between individuals with MCI and those with normal cognitive performance (10.89 *vs* 7.76 cm). Moreover, the relationship between NPC and MCI was investigated in a multivariable model after adjustment for potential confounders. The results of this analysis indicated that a remote NPC is an independent predictor of MCI in older adults.

In general, two hypotheses can be proposed regarding the relationship between the NPC and MCI. First, a set of afferent and efferent visual pathways located in various parts of the nervous system, including the brainstem, subcortical areas, frontal eye fields, and posterior-parietal cortical areas, are involved in the control of vergence eye movements[28]. Many of these nerve centers mutually play an essential role in cognition-related functions[29]. Therefore, age-related neurodegenerative changes in these nerve control centers can simultaneously manifest as vergence dysfunction (with receded NPC and poor gross convergence) and cognitive impairment.

The second hypothesis about the relationship between the NPC and MCI is the "disuse theory". There is an active cognitive reserve in the nervous system that depends primarily on some physiological features such as blood circulation, the number of synapses in the nervous system, and neurotransmitters[30]. On the other hand, a person's environmental conditions (daily life activities, job, education, *etc.*) significantly affect this active cognitive reserve by influencing neural processes and synaptic organization[31]. In fact, cognitive performance can be considered as a function of intrinsic physiological processes and environmental nurturing activities. According to the "disuse" theory, when an individual has a significant vision problem, the person's participation in many physical, perceptual, and social activities decreases, and this could lead to a reduction in active cognitive reserve and cognitive impairment over time[32]. Some evidence in the literature confirm this theory, and this theory has been frequently suggested for the relationship between visual impairment and cognitive impairment[32-34]. Observational studies have found that participation in activities that stimulate cognitive function (like reading and other near work) reduces the risk of cognitive impairment[35-36]. In addition, randomized clinical trials have reported that mental training programs and cognitive rehabilitation can boost cognitive performance in the elderly[37]. Regarding the role of "disuse" theory in the relationship between NPC and MCI, it should be said that many binocular vision disorders including convergence insufficiency (with receded NPC as the most prominent sign) are associated with multiple vision-related symptoms including eyestrain, headache, diplopia, sleepiness, blurred vision, and difficulty concentrating which are referred under the general term of asthenopic symptoms[38-39]. The occurrence of these asthenopic symptoms can lead a person to avoid performing visual activities aggravating these symptoms[40]. Therefore, avoiding near visual activities especially reading is commonly found in patients with vergence disorders[40] and this may be related to an increased risk of cognitive impairment according to the disuse theory.

In general, the association between NPC and MCI could be bidirectional; this relationship has important clinical implications regardless of its exact etiology. A receded NPC can be clinically proposed as a predictor of MCI in the elderly. Given the R square values of two multivariable models in the presence and absence of the NPC, it can be concluded that considering the NPC, in addition to the previously known risk factors, can increase the diagnostic ability of MCI by about 8%. The cutoff found in this study (>8.50 cm) can be used with acceptable sensitivity and specificity for this purpose. It is recommended that the elderly with a receded NPC>8.50 cm undergo detailed cognitive screening for a definite diagnosis of MCI. In this case, the necessary interventions can be carried out to slow down MCI progression to dementia. On the other hand, the results of the present report suggest convergence insufficiency as a possible risk factor for MCI. Therefore, convergence insufficiency in this age group should not be viewed as a simple anticipated binocular vision disorder. The importance of this issue is that convergence insufficiency has a high prevalence in older adults and in many cases, it is considered a normal age-related phenomenon and is not treated properly[17]. Future studies are recommended to investigate the relationship between convergence insufficiency and cognitive impairment, as well as the effect of convergence insufficiency treatment *via* vision therapy or base-in prism on cognitive performance.

The major strengths of the present report are the large sample size, population-based design, and robust control of confounders. However, this report has limitations. This report provides a cross-sectional view of the relationship between the NPC and MCI, and it is not possible to determine whether cognitive impairment occurred concurrently with or secondary to vergence dysfunction. We only used a single global cognitive test rather than a variety of specific tests measuring different domains of cognition. Another limitation is the lack of data on other sensory deprivations like hearing impairment that may also be related to cognitive impairment. It is recommended that the relationship between NPC and cognitive impairment be investigated in other populations considering the limitations of the present study.

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